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Full Papers

Syntheses of 4,5-Disubstituted Oxazoles via Regioselective C-4 Bromination

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Abstract:

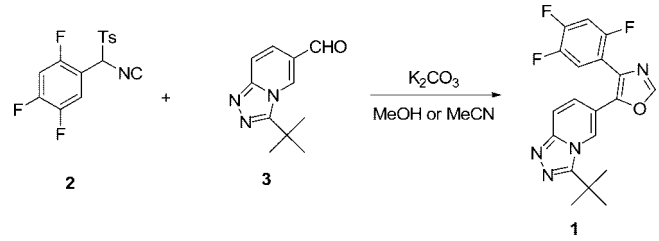
A scaleable and highly regioselective C-4 bromination of 5-substituted oxazoles is described. The use of DMF as solvent played a critical role in significantly improving the C-4/C-2 bromination ratio. The resulting 4-bromooxazoles were shown to be good Suzuki–Miyaura coupling partners with arylboronic acids. Furthermore, a simple and convenient method that employs triethylamine efficiently purged residual levels of palladium and iron to less than 10 ppm.

Introduction

Oxazoles with substitution at both C-4 and C-5 have recently attracted increased attention in the pharmaceutical community for their therapeutic potential in treating inflammation, cancer, and asthma[1,2] The 4,5-disubstituted oxazole **1** is a potent and selective inhibitor of the stress-activated kinase p38α.[3] It possesses good oral bioavailability in preclinical species and was expected to capture attributes of currently marketed rheumatoid arthritis therapies such as cyclooxygenase-II (COX-II) inhibitors and the antitumor necrosis factor (TNF) biological agents.[4]

The original synthesis of **1** (Scheme 1) condensed an aryl-substituted tosylmethylisocyanide **2**[5] with aldehyde **3**.[3] The condensation and cyclization proceeded in low yield following literature procedent.[6] Also extensive chromatographic purification was required to obtain **1** in suitable quality. This chemistry was not deemed scaleable due to the difficulty in the preparation of isocyanide **2** and its thermal instability. The thermal lability of isocyanide **2** is probably attributed to the additional fluorines[7] on the phenyl group. Therefore, we sought a more robust, efficient and scaleable synthesis.

Scheme 1



2 **3** **1**

Discussion

A number of syntheses of 4,5-disubstituted oxazoles[8] have been described in the literature, and the C-4 iodination method via 2-lithiooxazole (Scheme 2), as reported by Vedejs,[9] appeared most attractive to us as it allows the introduction of highly functionalized C-4 substituents. In this reaction (Scheme 2), the

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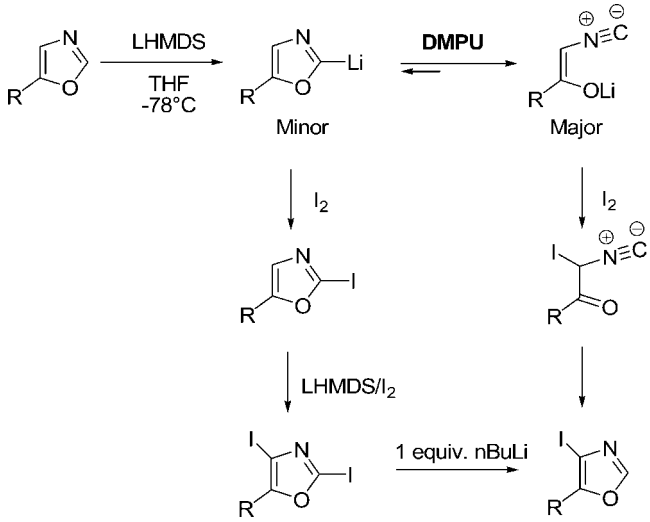
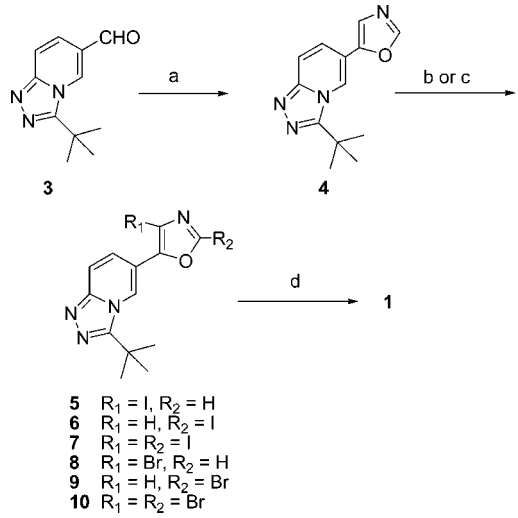
Scheme 2



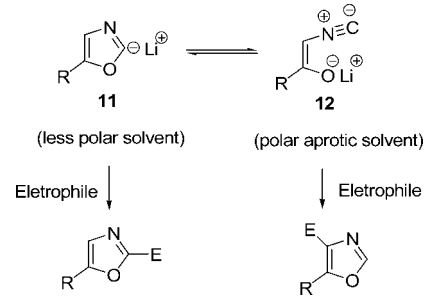
Scheme 3[a]



[a] (a) TosMIC, K_2CO_3, MeOH; (b) (1) LHMDS, DMPU/THF, −78 °C, (2) I_2 or NBS; (c) (1) LHMDS, DMF, –15 °C, then –70 °C, (2) NBS; (d) 2,4,5-trifluorophenylboronic acid, Pd(dppf)Cl_2·CH_2Cl_2, CsF, K_2CO_3, water/2-MeTHF.

initially formed 2-lithiooxazole tautomerized to the acyclic enolate with 1,3-dimethyl-tetrahydropyrimidin-2(1*H*)-one (DMPU) as reaction solvent. Trapping the acyclic lithio species with iodine gave the 4-iodooxazole as the major product. Both 2-iodooxazoles and 2,4-diiodooxazoles were formed as byproducts in the reaction. The latter could be treated with 1 equiv of *n*BuLi to generate the corresponding 4-iodooxazole. Thus, oxazole **4** (Scheme 3) was prepared by condensation[10] of commercially available tosylmethyl isocyanide (TosMIC) and

Scheme 4



aldehye **3**. Iodination of C-4 following the literature procedure gave modest yields (21–37%) of **5** and selectivity of ca. 4:1 in favor of **5** over **6**. Several other issues were noted during optimization of this reaction. First, the iodination reaction could not be driven to completion, despite the addition of excess reagents. The crude reaction mixture was typically contaminated with the starting material (20–26%) and di-iodooxazole **7** (5–10%). Silica gel chromatography was required to isolate the desired product. Second, a cost-effective alternative to DMPU as solvent (6 mL/g) would need to be identified prior to kilo campaigns. Finally, 4-iodooxazole **5** proved to be thermally unstable and therefore unsuitable going forward.

We envisioned some of the aforementioned issues could be addressed by preparing the 4-bromooxazole. Indeed, when NBS (1.0 equiv) was used as the electrophile under otherwise identical reaction conditions, the halogenation proceeded to completion, affording a 5:1 ratio of regioisomers **8** and **9** (Scheme 3), favoring the desired 4-bromooxazole **8**. The crude reaction mixture also contained 5% of dibromide **10**. After two crystallizations from methyl *tert*-butyl ether, **8** was isolated in 56% yield in >97% purity.[11] 4-Bromooxazole **8** showed good thermal stability; the compound decomposes at the DSC onset temperature of 198 °C.

It is known from the literature that the regioselectivity of this reaction is determined by the equilibrium between the 2-lithooxazole **11** and acyclic tautomer **12** (Scheme 4).[12,13] In polar aprotic solvents, the acyclic form is expected to predominate because of improved solvation. We envisioned that DMF, as a strongly polar aprotic solvent, would be an ideal choice to substitute for DMPU in this reaction. It is cheap and commercially available in anhydrous form, and most importantly, it has a low freezing point of −61 °C. Other common polar aprotic solvents were ruled out because of their high freezing points (DMAC, NMP, DMSO, DMI, acetonitrile), ability to react with anions (acetone, acetonitrile, DMSO), cost (DMI, DMPU), and worker safety and environmental concerns (HMPT, HMPA).[14]

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(11) Contaminated with <2% of the 2-bromoxazole **9** and <0.2% of the 2,4-dibromo **10**.

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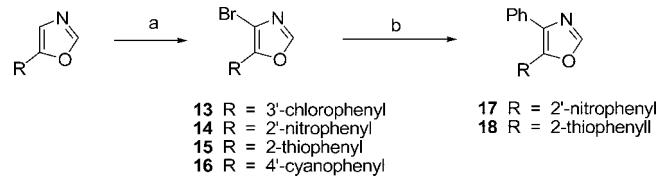
Our initial attempts to selectively brominate **4** employing DMF as solvent at −70 °C[15] gave poor to modest C-4/C-2 regioselectivity. We reasoned that the initially formed 2-lithiooxazole did not have ample opportunity to fully equilibrate to the acyclic form at low temperatures within the time scale of the reaction. We therefore decided to perform the lithiation at −15 °C and equilibrate the anion for 30 min before cooling to −70 °C and quenching with NBS. Employing these conditions, a regioselectivity of 98:2 favoring the desired C-4 bromide was obtained. Due to both the adiabatic temperature rise during the addition of the NBS and the highly exothermic bromination, it was necessary to lower the reaction temperature before the quench.[16] The product was isolated by crystallization (MTBE/hexanes) in 87% yield and contained less than 0.2% of 2-bromooxazole **9** as an impurity.[17] As expected, the lithium anions **11** and **12** behave similarly to stabilized enolates in that we were unable to detect any formylated products (from nucleophilic addition to DMF) in the reaction mixtures.

Having worked out a reliable preparation of 4-bromooxazole **8**, the last step proceeded without incident. Suzuki–Miyaura coupling of **8** with the commercially available 2,4,5-trifluorophenylboronic acid using $Pd(dppf)Cl_2$ as catalyst, CsF and K_2CO_3 in aqueous 2-MeTHF proceeded to completion in 1 h at 70 °C. The isolation of **1** from the reaction mixture proved to be difficult initially, due to the presence of the ferrocene ligand on the catalyst. Fortunately, the weak basicity of **1** rendered a unique solubility behavior of the compound. We discovered that **1** partitioned predominantly in the aqueous phase when distributed between aqueous HCl solution and toluene, yet it partitioned favorably in the organic phase when distributed between aqueous HCl and CH_2Cl_2. This provided an opportunity to clean up the reaction mixture with extractive manipulations that are detailed in the Experimental Section.

Another issue was removal of palladium from the final API. This is a topic that has received significant attention, and several common methods for Pd removal have been described in the literature.[18] For **1**, we rationalized that Pd was chelating through the weakly basic triazole moiety, and envisioned that treatment of **1** with a more basic amine (e.g., triethylamine) should displace palladium from **1** by competitive binding. This strategy was realized in practice; in the event, crude **1** (2100 ppm Pd, 3200 ppm Fe) was heated with a mixture of 3 mL/g of triethylamine and 2 mL/g of 2-propanol at reflux for 2–3 h. After cooling to 35 °C, addition of water (20–25 mL/g) crystallized the product out of solution. After a single repetition, **1** was isolated in 99.74% purity by HPLC with a Pd level of 9.0 ppm and Fe at 8.85 ppm.

The regioselective C-4 bromination, outline above, was applied to a series of C-5 substituted aryl and heteroaryl oxazoles (Scheme 5). We note that both the thiophene and nitrile moieties (**15** and **16**, respectively) remained intact under the reaction conditions. Subsequent Suzuki–Miyaura coupling reactions with phenylboronic acid proceeded uneventfully.

Scheme 5[a]



[a] (a) (1) LHMDS, –15 °C → –70 °C, DMF, (2) NBS; (b) $PhB(OH)_2$, $Pd(dppf)Cl_2$, CsF, K_2CO_3, water/2-MeTHF.

In summary, we have described a highly regioselective bromination at C-4 of 5-substituted oxazoles. The use of DMF as solvent and aging of the lithiated oxazole is critical to drive the equilibrium in favor of the acyclic isonitrile enolate, resulting in significantly improved C4/C2 regioselectivity. These 4-bromooxazoles were shown to be good Suzuki–Miyaura coupling partners with arylboronic acids. The bromination protocol was demonstrated on multikilogram scale supporting the development of **1**. Finally, we have demonstrated that the use of triethylamine is effective in purging residual palladium and iron from the Suzuki–Miyaura coupled product.

Experimental Section

General. NMR chemical shifts are reported in part per million (ppm) with TMS as an internal standard. LCMS was recorded using API-ES ionization mode. Reagents and solvents were obtained from commercial sources and used without further purifications. Achiral HPLC analyses were carried out using Agilent SB-CN columns (4.6 mm × 250 mm) with acetonitrile/0.2% perchloric acid aqueous buffer (20/80 or 40/60) as mobile phase (2 mL/min) and detection at 210 nm wavelength. HPLC purity is reported by area %.

3-*tert*-Butyl-6-(oxazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridine(4). 3-*tert*-Butyl-[1,2,4]triazolo[4,3-*a*]pyridine-6-carbaldehyde **3**[3] (5.08 kg, 25.0 mol), K_2CO_3 (6.05 kg, 43.8 mol) and tosylmethylisocyanide (4.88 kg, 25.0 mol) in methanol (106 L) was heated to 64–66 °C for 4 h. Water (54 L) was added, and methanol was removed under vacuum. The reaction was cooled to 20 °C and allowed to granulate overnight. The mixture was filtered, washed with water, and dried under full vacuum at 45 °C for 20 h to afford the product **4** (4.25 kg, 17.5 mol, 70% yield) as a yellow solid: HPLC purity 99.8%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 9H), 7.41 (s, 1H), 7.43 (d, J = 9.6 Hz, 1H), 7.81 (d, J = 9.6 Hz, 1H), 7.97 (s, 1H), 8.46 (s, 1H).

6-(4-Bromooxazol-5-yl)-3-*tert*-butyl-[1,2,4]triazolo[4,3-*a*]pyridine (8). To a reactor were charged **4** (3.5 kg, 14.4 mol) and anhydrous DMF (14 L). The resulting solution was cooled to −15 °C, and 1 N LHMDS in THF (1.05 equiv, 13.1 Kg) was then added. The reaction was stirred at −15 °C for 30 min and then cooled to −70 °C. A solution of NBS (2.57 kg, 14.4 mol) in DMF (7 L) was added while maintaining the temperature below −60 °C. The reaction was stirred for 30 min at the

(15) Although the freezing point of DMF is −61 °C, the reaction mixture had a freezing point of < −70 °C.
(16) Quenching the reaction at −15 °C with NBS led to a ca. 2/1 ratio of regioisomers, favoring the C-4 product. NBS was added as a solution in DMF (2.7 mL/g of NBS) at room temperature. Pre-cooling of the NBS solution would be desirable, but it reduced the solubility significantly. More studies are needed to determine if the anion quench can be adapted in a flow reactor under non-cryogenic conditions.
(17) A trace amount (<1%) of the dibromide **10** was observed in the reaction but was purged during the isolation of **8**.

same temperature and quenched by addition of 2 N aqueous NaOH solution (62 L). The reaction was extracted with CH_2Cl_2 (3 × 30 L). The combined organic extract was washed with 0.5 N NaOH solution and brine solution. The solution was concentrated, and solvent-exchanged with MTBE (18 L). Hexanes (18 L) was added, and the resulting slurry was granulated for 2 h at room temperature. The product was collected by filtration and dried at 40 to 50 °C under full vacuum to give 4.04 kg (12.6 mol, 87%) of **8** as an off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 9H), 7.78 (d, J = 9.6 Hz, 1H), 7.93 (d, J = 9.6 Hz, 1H), 7.97 (s, 1H), 8.93 (s, 1H). LCMS: 321 (M + 1), 322 (M + 2).

3-*tert*-Butyl-6-(4-(2,4,5-trifluorophenyl)oxazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridine (1). A mixture of **8** (3.0 kg, 9.34 mol), CsF (141 g, 0.93 mol), K_2CO_3 (1.55 kg, 11.2 mol), 2,4,5-trifluorophenylboronic acid (1.80 kg, 10.2 mol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ complex (374 g) in water (4.5 L) and 2-MeTHF (45 L) was heated to 70 °C for 1 h. 2-MeTHF was removed by distillation under reduced pressure. The resulting mixture was partitioned between 2 N aqueous HCl (30 L) and CH_2Cl_2 (48 L). The product-rich CH_2Cl_2 layer was concentrated atmospherically and displaced with toluene (45 L). This was followed by addition of 4 N HCl (30 L), which took the product to the aqueous phase. The product-rich aqueous layer was separated, and the pH was adjusted to 10 with 50 wt % NaOH. The crude product that crystallized out was collected by filtration. The palladium purging and polymorph conversion were carried out as follows. The crude product was treated with isopropanol (6 L) and TEA (9 L) at reflux for 3 h. After cooling to 35 °C, water (75 L) was charged. The batch was then cooled to 15 °C and filtered. The wet filter cake was charged back to the reactor, and the treatment was repeated. After cooling to 35 °C, water (75 L) was added. The batch was then cooled to 15 °C and filtered. After drying under vacuum, 3.08 kg (8.28 mol, 88.7% yield) of the desired product was isolated. Isopropanol (76 L) was added, and the resulting slurry was distilled to remove approximately 5 L of solvent to ensure no water was present. The solution was then cooled to 50 °C and filtered via a 0.2 μm filter for a particle-free operation. The filtrate was concentrated under partial vacuum to a final volume of 24 L. The concentration was then continued atmospherically to a final volume of approximately 6 L. The batch was cooled to 22 °C, stirred for 48 h, filtered and dried to afford 2.83 kg of **1** as a white solid (7.60 mol, 91.9% recovery). The material was of 99.74% purity with Pd and Fe at 7.86 and 11.95 ppm, respectively. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9H), 7.09–7.45 (m, 1H), 7.48 (d, J = 9.6 Hz, 1H), 7.53–7.62 (m, 1H), 8.04 (d, J = 9.6 Hz, 1H), 8.11 (s, 1H), 8.42 (s, 1H). LCMS 374 (M + 2), 373 (M + 1).

4-Bromo-5-(3-chlorophenyl)oxazole (13). Following the same procedure as described for the synthesis of **8**, 5.31 g was prepared in 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.74 (t, J = 1.7 Hz, 1H), 7.70 (s, 1H), 7.66 (dt, J = 7.1, 1.7 Hz, 1H), 7.24–7.17 (m, 2H). MS *m/z* 257.9 (M + H). HRMS $C_9H_6BrClNO$ (M + H^+) calcd 257.9326; found 257.9321.

4-Bromo-5-(2-nitrophenyl)oxazole (14). Following the same procedure as described for 4-bromooxazole **8**, 4.44 g was prepared in 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.5 Hz, 1H), 7.74 (s, 1H), 7.61–7.54 (m, 2H), 7.47 (t, J = 7.9 Hz, 1H). MS *m/z* 269.0 (M + H). HRMS $C_9H_6BrN_2O_3$ (M + $H^{+)}$ calcd 268.9562; found 268.9560.

4-Bromo-5-(thiophen-2-yl)oxazole (15). Following the same procedure as described for 4-bromooxazole **8**, 12.13 g was prepared in 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.63 (dd, J = 3.7, 0.9 Hz, 1H), 7.45 (dd, J = 5.0, 0.9 Hz, 1H), 7.63 (dd, J = 5.0, 3.7 Hz, 1H). MS *m/z* 229.8 (M + H^+). HRMS C_7H_5BrNO (M + $H^{+)}$ calcd 229.9275; found 229.9284.

4-Bromo-5-(4-cyanophenyl)oxazole (16). Following the same procedure as described for 4-bromooxazole **8**, 4.44 g was prepared in 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.77 (m, 4H), 7.67 (S, 1H). MS *m/z* 248.95 (M – H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.02, 136.60, 133.06, 129.46, 125.97, 125.53, 117.81, 113.84, 108.42.

5-(2-nitrophenyl)-4-phenyloxazole (17). To a 100-mL round-bottomed flask were charged 4-bromo-5-(2-nitrophenyl)-oxazole (2.0 g, 7.43 mmol), cesium fluoride (0.113 g, 0.743 mmol), potassium carbonate (1.23 g, 8.92 mmol), phenylboronic acid (2.0 g, 15.6 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ complex (0.341 g, 0.409 mmol), water (3 mL), and 2-methyl THF (30 mL). The mixture was heated to 75 °C under nitrogen atmosphere and held for 18 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and water (20 mL). The organic layer was separated and washed with HCl aqueous (0.5%, 20 mL) and brine (20 mL). The organic solution was concentrated, and the crude was purified with flash chromatography to give 1.21 g (61%) of **17** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (m, 1H), 8.01 (s, 1H), 7.66–7.63 (m, 2H), 7.61–7.55 (m, 5H), 7.36–7.31 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.998, 141.428, 133.544, 132.543, 131.009, 130.957, 128.972, 128.680, 127.335, 125.458. MS *m/z* 267.1 (M + H). HRMS $C_{15}H_{11}N_2O_3$ (M + H^+) calcd 267.0770; found 267.0768.

4-Phenyl-5-(thiophen-2-yl)oxazole (18). Following the same procedures described above, a mixture of 4-bromo-5-(thiophen-2-yl)oxazole (10.0 g, 0.0435 mol), cesium fluoride (0.660 g, 0.00435 mol), potassium carbonate (14.4 g, 0.104 mol), phenylboronic acid (11.7 g, 0.0913 mol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ complex (1.99 g, 0.00239 mol) in water (15 mL) and 2-methyl THF (150 mL) was heated to 75 °C under nitrogen atmosphere for 16 h. The reaction mixture was

(18) (a) Some examples of palladium purging methods: Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T. *Org. Process Res. Dev.* **2005**, *9*, 198–205. (b) Koenigsberger, K.; Chen, G.-P.; Wu, R. R.; Girgis, M. J.; Prasad, K.; Repic, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2003**, *7*, 733–742. (c) Chen, C.-Y.; Dagneau, P.; Grabowski, E. J. J.; Oballa, R.; O'Shea, P.; Prasit, P.; Robichaud, J.; Tillyer, R.; Wang, X. *J. Org. Chem.* **2003**, *68*, 2633–2638. (d) Urawa, Y.; Miyazawa, M.; Ozeki, N.; Ogura, K. *Org. Process Res. Dev.* **2003**, *7*, 191–195. (e) Ishihara, K.; Nakayama, M.; Kurihara, H.; Itoh, A.; Haraguchi, H. *Chem. Lett.* **2000**, *10*, 1218–1219. (f) Rosso, V. W.; Lust, D. A.; Bernot, P. J.; Grosso, J. A.; Modi, S. P.; Rusowicz, A.; Sedergran, T. C.; Simpson, J. H.; Srivastava, S. K.; Humora, M. J.; Anderson, N. G. *Org. Process Res. Dev.* **1997**, *1*, 311–314.

cooled to room temperature and diluted with ethyl acetate (200 mL) and water (100 mL). The ethyl acetate layer was separated and washed with HCl (0.5%, 100 mL) and brine. The organic solution was concentrated and purified with flash chromatography to yield 5.33 g (54%) of **18** as an pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.95 (s, 1H), 7.82–7.79 (m, 2H), 7.40–7.36 (m, 5H), 7.09–7.06 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 149.903, 141.589, 134.979, 129.806, 128.923, 128.830, 128.243, 127.884, 127.017, 126.748120.206, 115.858. MS *m/z* 228.0 (M + H). HRMS $C_{13}H_{10}NOS$ ($M + H^+$) calcd 268.0483; found 228.0479.

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Supporting Information Available

Characterization spectra. This information is available free of charge via the Internet at http://pubs.acs.org.

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